IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Jean-Luc Balligand et al. Group Art Unit: TBA

Serial No.: TBA Examiner: TBA

Filed: February 11, 2002

For: NOVEL PHARMACEUTICAL COMPOSITOINS FOR MODULATING ANGIOGENESIS

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend the claims as follows:

3. (Amended) A compound according to claim 1 for use as a medicament for the modulation of angiogenesis, wherein said compound modulates intracellular free cholesterol by acting on cholesterol synthesis, cholesterol metabolism, cholesterol influx or cholesterol efflux.

4. (Amended) A compound according to claim 1 for use as a medicament for the modulation of angiogenesis, wherein said compound influences cholesterol metabolism and decreases caveolin-1 abundance and is chosen from the group comprising HMGCoA reductase inhibitors or a pharmacologically acceptable derivative thereof.

7. (Amended) A compound according to claim 1 for use as a medicament for the modulation of angiogenesis, wherein said compound influences cholesterol metabolism and increases caveolin-1 abundance, is chosen from a group comprising ACAT inhibitors or a pharmacologically acceptable derivative thereof.

9. (Amended) A compound according to claim 1 for use as a medicament for the modulation of angiogenesis wherein said compound increases the export of cholesterol out of peripheral cells through the increased abundance of HDL particles resulting in the modulation of caveolin-1.

11. (Amended) A compound according to claim 1 for use as a medicament for the modulation of angiogenesis wherein said compound decreases the production of cholesterol-rich VLDL particles by the liver.

13. (Amended) A compound according to claim 1 for use as a medicament for the modulation of angiogenesis wherein said compound influences abundance and/or activity of caveolin-l, eNOS, Hsp90 or calmodulin.

21. (Amended) A compound according to claim 13 for use as a medicament for the modulation of angiogenesis, which is able to trap the endogenous caveolin-1 preventing its binding to the endothelial isoform nitric oxide synthase (eNOS).

22. (Amended) A compound according to claim 13 for use as a medicament for the modulation of angiogenesis which is a nucleic add encoding the partial or total amino acid sequence of eNOS or the eNOS sequence deleted or mutated in the active caveolin binding site or an analogue thereof which can increase the concentration of unbound (activated) eNOS.

27. (Amended) A pharmacological composition comprising a compound according to claim 1 or a pharmacologically acceptable derivative thereof for the stimulation or inhibition of angiogenesis.

28. (Amended) Use of a compound according to claim 1, optionally combined with a suitable excipient, for the treatment of angiogenesis related diseases such as angiogenesis-dependent

tumor growth and metastatic diseases, ischemic heart and peripheral vascular diseases including cerebral diseases and wound healing.

31. (Amended) Method to manufacture a medicament for the modulation of angiogenesis comprising a compound according to claim 1.

32. (Amended) Method of treating a subject in the need of influencing angiogenesis by administering an angiogenesis-modulating-compound according to claim 1 in a sufficient concentration able to modulate angiogenesis within this subject.

33. (Amended) Use of a compound according to claim 1 for the modulation of the cholesterol metabolism in a cell in vitro, in vivo or ex vivo.

34. (Amended) Use of a compound according to claim 1 for the modulation of the expression of caveolin-l in a cell in vitro, in vivo or ex vivo. 25

35. (Amended) Use of a compound according to claim 1 for the modulation of the expression of eNOS in a cell in vitro, in vivo or ex vivo.

36. (Amended) Use of a compound according to claim 1 for the modulation of the 30 expression of calmodulin in a cell in vitro, in vivo or ex vivo.

37. (Amended) Use of a compound according to claim 1 for the expression of Hsp90 in a cell in vitro, in vivo or ex vivo.

REMARKS

The amendments to the claims have been made to remove the multiple dependencies of the claims.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: DCLERC-2 P1

Date: February 11, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the claims as follows:

3. (Amended) A compound according to [claims 1 or 2] claim 1 for use as a medicament for the modulation of angiogenesis, wherein said compound modulates intracellular free cholesterol by acting on cholesterol synthesis, cholesterol metabolism, cholesterol influx or cholesterol efflux.

4. (Amended) A compound according to [any of the claims 1 to 3] claim 1 for use as a medicament for the modulation of angiogenesis, wherein said compound influences cholesterol metabolism and decreases caveolin-1 abundance and is chosen from the group comprising HMGCoA reductase inhibitors or a pharmacologically acceptable derivative thereof.

7. (Amended) A compound according to [any of the claims 1 to 3] claim 1 for use as a medicament for the modulation of angiogenesis, wherein said compound influences cholesterol metabolism and increases caveolin-1 abundance, is chosen from a group comprising ACAT inhibitors or a pharmacologically acceptable derivative thereof.

9. (Amended) A compound according to [any of the claims 1 to 3] claim 1 for use as a medicament for the modulation of angiogenesis wherein said compound increases the export of cholesterol out of peripheral cells through the increased abundance of HDL particles resulting in the modulation of caveolin-1.

11. (Amended) A compound according to [any of the claims 1 to 3] claim 1 for use as a medicament for the modulation of angiogenesis wherein said compound decreases the production of cholesterol-rich VLDL particles by the liver.

13. (Amended) A compound according to [any of the claims 1 to 2] claim 1 for use as a medicament for the modulation of angiogenesis wherein said compound influences abundance and/or activity of caveolin-1, eNOS, Hsp90 or calmodulin.

21. (Amended) A compound according to [claims 13 and 20] claim 13 for use as a medicament for the modulation of angiogenesis, which is able to trap the endogenous caveolin-1 preventing its binding to the endothelial isoform nitric oxide synthase (eNOS).

22. (Amended) A compound according to claim 13 [and 20] for use as a medicament for the modulation of angiogenesis which is a nucleic add encoding the partial or total amino acid sequence of eNOS or the eNOS sequence deleted or mutated in the active caveolin binding site or an analogue thereof which can increase the concentration of unbound (activated) eNOS.

27. (Amended) A pharmacological composition comprising a compound according to [any of the claims 1 to 26] claim 1 or a pharmacologically acceptable derivative thereof for the stimulation or inhibition of angiogenesis.

28. (Amended) Use of a compound according to [claims 1 to 26] claim 1, optionally combined with a suitable excipient, for the treatment of angiogenesis related diseases such as angiogenesis-dependent tumor growth and metastatic diseases, ischemic heart and peripheral vascular diseases including cerebral diseases and wound healing.

31. (Amended) Method to manufacture a medicament for the modulation of angiogenesis comprising a compound according to [any of the claims 1 to 26] claim 1.

32. (Amended) Method of treating a subject in the need of influencing angiogenesis by administering an angiogenesis-modulating-compound according to [claims 1 to 26] claim 1 in a sufficient concentration able to modulate angiogenesis within this subject.

33. (Amended) Use of a compound according to [claims 1 to 26] claim 1 for the modulation of the cholesterol metabolism in a cell in vitro, in vivo or ex vivo.

34. (Amended) Use of a compound according to [any of the claims 1 to 26] claim 1 for the modulation of the expression of caveolin-l in a cell in vitro, in vivo or ex vivo. 25

35. (Amended) Use of a compound according to [any of the claims 1 to 26] claim 1 for the modulation of the expression of eNOS in a cell in vitro, in vivo or ex vivo.

36. (Amended) Use of a compound according to [any of the claims 1 to 26] claim 1 for the modulation of the 30 expression of calmodulin in a cell in vitro, in vivo or ex vivo.

37. (Amended) Use of a compound according to [any of the claims 1 to 26] claim 1 for the expression of Hsp90 in a cell in vitro, in vivo or ex vivo.